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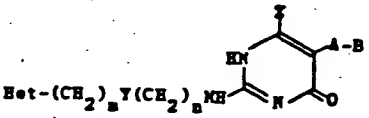
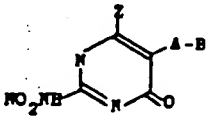
(54) Process for preparing 2-aminopyrimidones, intermediate 2-nitroaminopyrimidones and a process for their preparation.

(57) 2-Aminopyrimidones which are histamine H_2-antagonists having the structure



in which Het is a nitrogen-containing 5- or 6-membered fully unsaturated heterocyclic group, m is 0 or 1, Y is methylene, oxygen or sulphur, n is 2 or 3, Z is hydrogen or lower alkyl, A is an alkylene group or an alkylene group interrupted by oxygen or sulphur, and B is hydrogen or a methyl, cycloalkyl, heteroaryl, phenyl, naphthyl, benzodioxolyl or dihydrobenzodioxinyl group, are prepared by a process in which an amine $Het\text{-}(CH_2)_m\text{-}Y(CH_2)_n\text{-}NH_2$ is reacted with a 2-nitroaminopyrimidone of structure



The new 2-nitroaminopyrimidone intermediates are prepared by reacting nitroguanidine with an oxoester $RO_2C\text{-}CH(COZ)\text{-}A\text{-}B$ where R is lower alkyl.

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PROCESS FOR PREPARING 2-AMINOPYRIMIDONES, INTERMEDIATE 2-NITROAMINOPYRIMIDONES AND A PROCESS FOR THEIR PREPARATION

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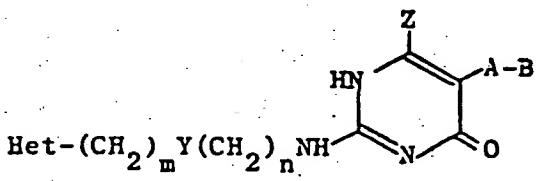
This invention relates to a chemical process for preparing 2-aminopyrimidones which have histamine H_2-antagonist activity, and to novel intermediates for use in this process and to a process for preparing them.

In German Offenlegungsschriften 2643670 and 2658267 there are described specific processes for preparing 2-aminopyrimidones which comprise reacting an amine with a pyrimidone which has a lower alkylthio, benzylthio or halogen group in the 2-position. We have found that a better process for preparing these 2-aminopyrimidones is to react an amine with a pyrimidone which has a nitroamino group in the 2-position.

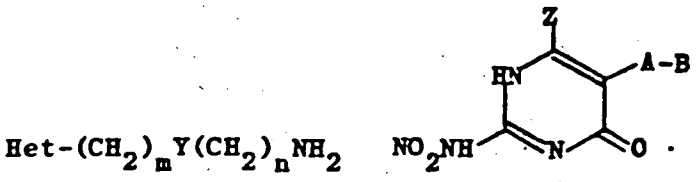
According to the invention there is provided a process for preparing a 2-aminopyrimidone of Structure 1:-



(1)

in which Het is a nitrogen-containing 5- or 6- membered fully unsaturated heterocyclic group which is optionally substituted by one or more lower alkyl, trifluoromethyl, halogen, hydroxy, lower alkoxy or amino groups which groups can be the same or different, m is 0 or 1, Y is methylene, oxygen or sulphur, n is 2 or 3; Z is hydrogen or lower alkyl (preferably methyl); A is C_1-C_5 alkylene or $-(CH_2)_p-W(CH_2)_q-$ where W is oxygen or sulphur and the sum of p and q is 1 to 4 and B is hydrogen, methyl, C_3-C_6 cycloalkyl, a heteroaryl group optionally substituted by one or more (which may be the same or different) lower alkyl or lower alkoxy groups, or B is a

naphthyl, 5- or 6-(2,3-dihydro-1,4-benzodioxinyl), or a 4- or 5-(1,3-benzodioxolyl) group, or a phenyl group optionally substituted with one or more (which may be the same or different) lower alkyl, lower alkoxy, halogen, aryl(lower alkoxy) (preferably benzyloxy), hydroxy, lower alkoxy-lower alkoxy, trifluoromethyl, di(lower alkyl)amino, phenoxy, halophenoxy, lower alkoxyphenoxy, phenyl, halophenyl or lower alkoxyphenyl groups; characterised in that an amine of Structure 2, in which Het, m, Y and n are as defined for Structure 1, is reacted with a 2-nitroaminopyrimidone of Structure 3, in which Z, A and B are



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as defined for Structure 1. A phenolic hydroxy group can, if desired, be protected during the reaction and subsequently regenerated. Examples of hydroxy protecting groups are methoxymethyl, methylthiomethyl, tetrahydropyranyl, benzyl, acyl and lower alkyl.

Throughout this specification by the terms 'lower alkyl' and 'lower alkoxy' are meant alkyl and alkoxy groups which can be straight or branched and which contain 1 to 4 carbon atoms. Particular lower alkyl groups are methyl, ethyl, 1-propyl and 2-propyl. Particular lower alkoxy groups are methoxy, ethoxy, 1-propoxy and 2-propoxy.

Examples of heterocycles of the group Het are imidazole, pyridine, thiazole, isothiazole, oxazole, isoxazole, triazole and thiadiazole. Preferably the group Het is linked to $(CH_2)_m$ by a carbon atom of the heterocycle adjacent to a

nitrogen atom. Examples of the group Het are 2- or 4-imidazolyl optionally substituted by lower alkyl (preferably methyl), halogen (preferably chlorine or bromine), trifluoromethyl or hydroxymethyl, 2-pyridyl optionally substituted by one or more (which can be the same or different) lower alkyl (preferably methyl), lower alkoxy (preferably methoxy), halogen (preferably chlorine or bromine), amino or hydroxy groups, 2-thiazolyl, 3-isothiazolyl optionally substituted by chlorine or bromine, 3-(1,2,5)-thiadiazolyl optionally substituted by chlorine or bromine, or 2-(5-amino-1,3,4-thiadiazolyl). Particular Het groups are 5-methyl-4-imidazolyl, 5-bromo-4-imidazolyl, 2-pyridyl, 3-methyl-2-pyridyl,3-methoxy-2-pyridyl, 3-ethoxy-2-pyridyl, 3,4-dimethoxy-2-pyridyl, 3-fluoro-2-pyridyl, 3-chloro-2-pyridyl, 3-bromo-2-pyridyl, 3-iodo-2-pyridyl, 3-bromo-4-methyl-2-pyridyl and 2-thiazolyl.

Examples of heteroaryl groups B are pyridyl, furyl, thienyl, thiazolyl, oxazolyl, isothiazolyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazyl, thiadiazolyl, quinolyl, isoquinolyl, 5,6,7,8-tetrahydroquinolyl, 1,3-dioxolopyridyl, benzimidazolyl and benzthiazolyl. Particular heteroaryl groups are 2-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 2-imidazolyl, 2-pyrimidyl, 2-pyrazyl, 3-pyridazyl, 3-quinolyl and 1-isoquinolyl optionally substituted by one or more lower alkyl or lower alkoxy groups. Specific heteroaryl groups are 2-furyl, 3-pyridyl, 6-methyl-3-pyridyl, 5,6-dimethyl-3-pyridyl, 6-methoxy-3-pyridyl, 2-methoxy-4-pyridyl and 4-methoxy-2-pyridyl.

Specific substituted phenyl groups B are 3-chlorophenyl, 3,4-dichlorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl and 3,4,5-trimethoxyphenyl.

PREPARATION 9

2,3-Dihydro-1,4-benzodioxin-6-carboxaldehyde (m.p. 41-43°, prepared by reacting 3,4-dihydroxybenzaldehyde with ethanedisulphonic acid dimethyl ester and potassium hydroxide) was condensed with monoethyl malonate in pyridine with piperidine as catalyst to give ethyl 3-(6-(2,3-dihydro-1,4-benzodioxinyl)-acrylate, m.p. 49-53°, which was reduced with hydrogen and palladium-on-charcoal, and the product was reacted with ethyl formate and sodium hydride in 1,2-dimethoxyethane to give ethyl 2-formyl-3-[6-(2,3-dihydro-1,4-benzodioxinyl)]propionate as an oil.

PREPARATION 10

A mixture of ethyl 3-(1-naphthyl)propionate (18.01 g) and ethyl formate (8.88 g) was added to a suspension of sodium hydride (57% dispersion in oil, 4.43 g) in 1,2-dimethoxyethane stirred at 5°, and the mixture was stirred at 5° for one hour and allowed to warm to room temperature. Water (300 ml) was added and the mixture was extracted with chloroform and the residual aqueous phase adjusted to pH 4 with hydrochloric acid: the mixture was extracted with ether and the extracts evaporated to give ethyl 2-formyl-3-(1-naphthyl)-propionate (16.05 g) as an oil.

PREPARATION 11

(i) A solution of sodium methoxide (from 0.535 g sodium) in dry methanol (40 ml) was added dropwise to a stirred suspension of 3-fluoro-2-methyl-4-nitropyridine N-oxide (2 g) in dry methanol (50 ml) and the mixture was stirred overnight. Additional sodium methoxide (from 0.053 g sodium) was added and the mixture was heated under reflux for 1 hour. The mixture was neutralised with hydrochloric acid and evaporated to dryness. The residue was extracted with chloroform and the extract was evaporated to dryness to give 3,4-dimethoxy-2-methylpyridine N-oxide.

(ii) Trifluoroacetic anhydride (4.0 ml) was added dropwise to a stirred solution of 3,4-dimethoxy-2-methylpyridine N-oxide (1.91 g) in dichloromethane (25 ml) and the mixture was left to stand at room temperature for 8 days during which time trifluoroacetic anhydride (4.77 ml) was added in two portions. The mixture was evaporated to dryness and the residue was purified by extracting a chloroform solution with aqueous sodium bicarbonate and elution from silica gel with methanol-chloroform (1:9) to give 2-hydroxymethyl-3,4-dimethoxypyridine (1.6 g).

(iii) 2-Hydroxymethyl-3,4-dimethoxypyridine was reacted with thionyl chloride in chloroform to give 2-chloromethyl-3,4-dimethoxypyridine hydrochloride, m.p. 158-9° (decomp), which was reacted with cysteamine hydrochloride and sodium ethoxide in ethanol to give 2-(3,4-dimethoxy-2-pyridylmethylthio)-ethylamine.

EXAMPLE 1

Sodium (1.15 g) was dissolved in methanol (50 ml) and nitroguanidine (4.7 g) was added to the cooled solution. The mixture was heated under reflux for 45 minutes, ethyl 2-formyl-3-(3-pyridyl)propionate (9.3 g) was added portionwise and the mixture was heated under reflux for 45 hours and evaporated to dryness. Water was added to the residue and the mixture was extracted with chloroform. The residual aqueous phase was adjusted to pH 5 with acetic acid, and the solid which was precipitated was filtered off, washed and dried to give 2-nitroamino-5-(3-pyridylmethyl)-4-pyrimidone, m.p. 214.5-216°, in 38% yield.

EXAMPLE 2

A solution of ethyl 2-formyl-3-(6-methyl-3-pyridyl)-propionate (1.55 g) in methanol (20 ml) was added to a stirred solution of sodium methoxide (from 0.161 g sodium) in methanol (20 ml). Dried nitroguanidine (0.73 g) was added and the mixture was heated under reflux overnight and evaporated